JACC: ASIA VOL. 2, NO. 3, 2022

ORIGINAL RESEARCH

Modifiers of the Risk of Diabetes for Long-Term Outcomes After Coronary Revascularization

CREDO-Kyoto PCI/CABG Registry

Kyohei Yamaji, MD,[a] Hiroki Shiomi, MD,[b] Takeshi Morimoto, MD,[c] Yukiko Matsumura-Nakano, MD,[b] Natsuhiko Ehara, MD,[d] Hiroki Sakamoto, MD,[e] Yasuaki Takeji, MD,[b] Yusuke Yoshikawa, MD,[b] Ko Yamamoto, MD,[b] Eri T. Kato, MD,[b] Kazuaki Imada, MD,[a] Takeshi Tada, MD,[f] Ryoji Taniguchi, MD,[g] Ryusuke Nishikawa, MD,[e] Tomohisa Tada, MD,[e] Takashi Uegaito, MD,[h] Tatsuya Ogawa, MD,[i] Miho Yamada, MD,[j] Teruki Takeda, MD,[k] Hiroshi Eizawa, MD,[l] Nobushige Tamura, MD,[m] Keiichi Tambara, MD,[n] Satoru Suwa, MD,[o] Manabu Shirotani, MD,[p] Toshihiro Tamura, MD,[q] Moriaki Inoko, MD,[r] Junichiro Nishizawa, MD,[s] Masahiro Natsuaki, MD,[t] Hiroshi Sakai, MD,[u] Takashi Yamamoto, MD,[u] Naoki Kanemitsu, MD,[v] Nobuhisa Ohno, MD,[w] Katsuhisa Ishii, MD,[x] Akira Marui, MD,[y] Hiroshi Tsuneyoshi, MD,[z] Yasuhiko Terai, MD,[aa] Shogo Nakayama, MD,[bb] Kazuhiro Yamazaki, MD,[cc] Mamoru Takahashi, MD,[dd] Takashi Tamura, MD,[ee] Jiro Esaki, MD,[ff] Shinji Miki, MD,[gg] Tomoya Onodera, MD,[hh] Hiroshi Mabuchi, MD,[k] Yutaka Furukawa, MD,[d] Masaru Tanaka, MD,[ii] Tatsuhiko Komiya, MD,[jj] Yoshiharu Soga, MD,[y] Michiya Hanyu, MD,[kk] Takenori Domei, MD,[a] Kenji Ando, MD,[a] Kazushige Kadota, MD,[f] Kenji Minatoya, MD,[cc] Yoshihisa Nakagawa, MD,[u] Takeshi Kimura, MD,[b] on behalf of the CREDO-Kyoto PCI/CABG Registry Investigators

ABSTRACT

BACKGROUND Diabetes is a well-known risk factor for adverse outcomes after coronary revascularization.

OBJECTIVES This study sought to determine high-risk subgroups in whom the excess risks of diabetes relative to nondiabetes are particularly prominent and thus may benefit from more aggressive interventions.

METHODS The study population consisted of 39,427 patients (diabetes: n = 15,561; nondiabetes: n = 23,866) who underwent first percutaneous coronary intervention (n = 33,144) or coronary artery bypass graft (n = 6,283) in the pooled CREDO-Kyoto PCI/CABG (Coronary Revascularization Demonstrating Outcome Study in Kyoto Percutaneous Coronary Intervention/Coronary Artery Bypass Graft) registry. The primary outcome measure was major adverse cardiovascular and cerebral endpoints (MACCE), which was defined as a composite of all-cause death, myocardial infarction, and stroke.

RESULTS With median follow-up of 5.6 years, diabetes was associated with significantly higher adjusted risks for MACCE. The excess adjusted risks of diabetes relative to nondiabetes for MACCE increased with younger age (≤64 years: adjusted HR: 1.30; 95% CI: 1.19-1.41; $P < 0.001$; 64-73 years: adjusted HR: 1.24; 95% CI: 1.16-1.33; $P < 0.001$; >73 years: adjusted HR: 1.17; 95% CI: 1.10-1.23; $P < 0.001$; $P_{interaction} < 0.001$), mainly driven by greater excess adjusted mortality risk of diabetes relative to nondiabetes in younger tertile. No significant interaction was observed between adjusted risk of diabetes relative to nondiabetes for MACCE and other subgroups such as sex, mode of revascularization, and clinical presentation of acute myocardial infarction.

CONCLUSIONS The excess risk of diabetes relative to nondiabetes for MACCE was profound in the younger population. This observation suggests more aggressive interventions for secondary prevention in patients with diabetes might be particularly relevant in younger patients. (JACC: Asia 2022;2:294-308) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2021.12.012

Despite recent advances in the treatment of diabetes, diabetes remains an established risk factor for adverse macrovascular and microvascular events in the general population,[1-5] as well as in patients with either established atherosclerosis or significant risk factors for atherosclerosis.[6,7] Cardiovascular disease is a leading cause of death in patients with diabetes, reinforcing the need for aggressive cardiovascular risk reduction in this population, especially among those who already have atherosclerotic cardiovascular disease. Coronary revascularization is often needed in patients with diabetes, and it is well known that patients with diabetes, compared with those without, have higher risk for adverse cardiovascular events after coronary revascularization.[6-9] However, it remains unclear whether there are some patient subgroups in whom the excess risks of diabetes relative to nondiabetes are particularly prominent for adverse clinical outcomes after coronary revascularization and thus may benefit from more aggressive interventions for secondary prevention. Therefore, we aimed to identify the factors that modify the cardiovascular and noncardiovascular risk of diabetes relative to nondiabetes after coronary revascularization with percutaneous coronary intervention (PCI) or with coronary artery bypass graft (CABG) in a large-scale Japanese pooled population.

ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

CABG = coronary artery bypass graft

MACCE = major adverse cardiovascular and cerebral endpoints

MI = myocardial infarction

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

TVR = target vessel revascularization

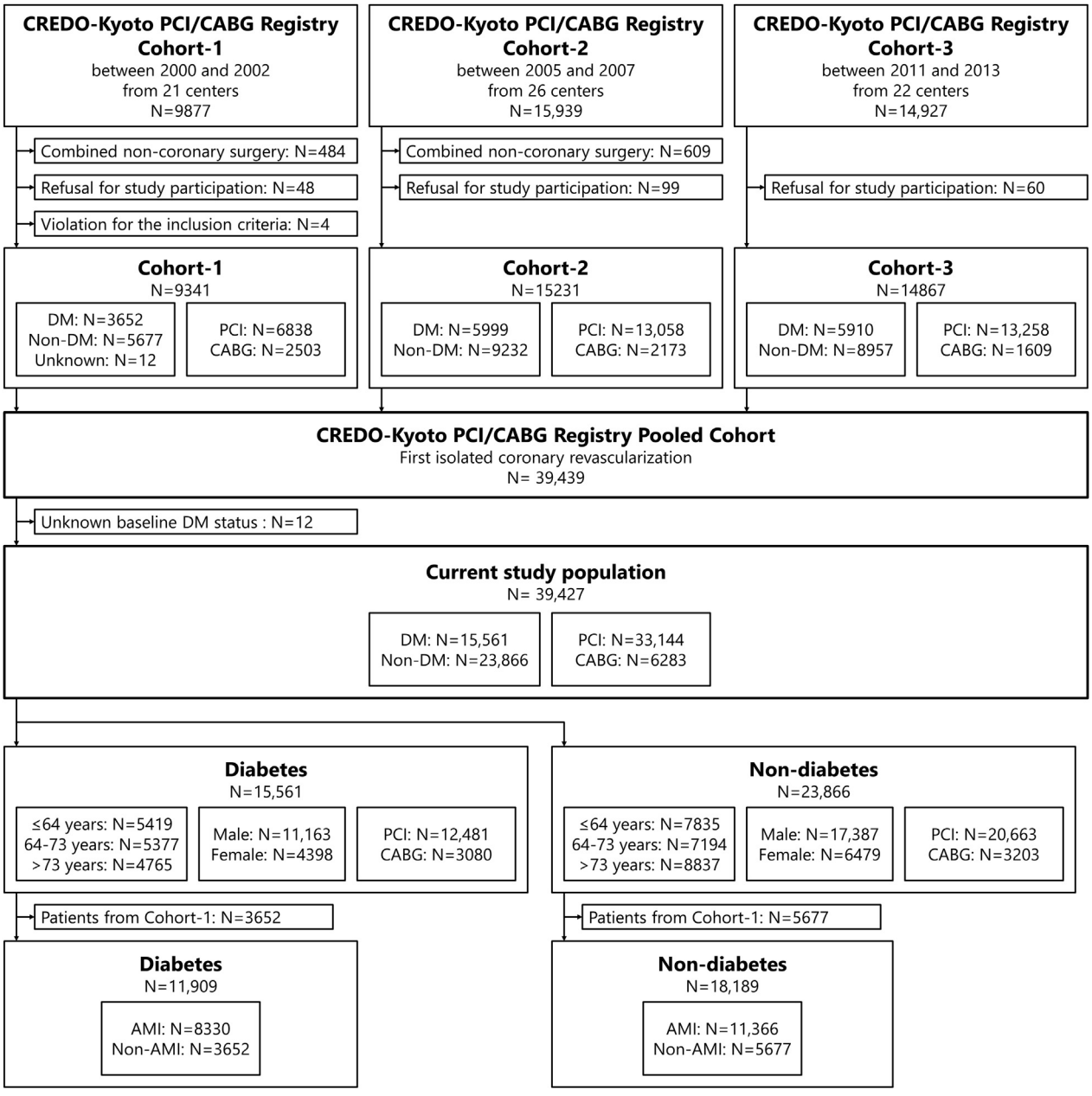
METHODS

STUDY POPULATION. The CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) PCI/CABG registry cohorts 1, 2, and 3 are a series of physician-initiated, non-company-sponsored, multicenter registries enrolling consecutive patients who underwent first coronary revascularization with PCI or CABG in Japan. We enrolled only patients with stable coronary artery disease in cohort 1, excluding those with acute myocardial infarction (AMI) within a week before the index procedure. Cohort 1 enrolled 9,877 patients from 21 centers between January 1, 2000, and December 31, 2002, in the bare-metal stent era.[10] Cohort 2 enrolled 15,939 patients from 26 centers between January 1, 2005, and December 31, 2007, after the introduction of drug-eluting stents in 2004.[11] Cohort 3 enrolled 14,927 patients from 22 centers between January 1, 2011, and December 31, 2013, after the approval of new-generation drug-eluting stents in 2010

From the [a]Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan; [b]Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan; [c]Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Japan; [d]Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, Kobe, Japan; [e]Department of Cardiology, Shizuoka General Hospital, Shizuoka, Japan; [f]Department of Cardiology, Kurashiki Central Hospital, Kurashiki, Japan; [g]Department of Cardiology, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan; [h]Department of Cardiology, Kishiwada City Hospital, Kishiwada, Japan; [i]Department of Cardiovascular Surgery, Kishiwada City Hospital, Kishiwada, Japan; [j]Department of Cardiology, Hamamatsu Rosai Hospital, Hamamatsu, Japan; [k]Department of Cardiology, Koto Memorial Hospital, Higashiomi, Japan; [l]Department of Cardiology, Kobe City Nishi-Kobe Medical Center, Kobe, Japan; [m]Department of Cardiovascular Surgery, Kindai University Nara Hospital, Ikoma, Japan; [n]Department of Cardiovascular Surgery, Juntendo University Shizuoka Hospital, Izunokuni, Japan; [o]Department of Cardiology, Juntendo University Shizuoka Hospital, Izunokuni, Japan; [p]Department of Cardiology, Kindai University Nara Hospital, Ikoma, Japan; [q]Department of Cardiology, Tenri Hospital, Tenri, Japan; [r]Department of Cardiology, The Tazuke Kofukai Medical Research Institute, Kitano Hospital, Osaka, Japan; [s]Department of Cardiovascular Surgery, Hamamatsu Rosai Hospital, Hamamatsu, Japan; [t]Department of Cardiovascular Medicine, Saga University, Saga, Japan; [u]Department of Cardiology, Shiga University of Medical Science Hospital, Otsu, Japan; [v]Department of Cardiovascular Surgery, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan; [w]Department of Cardiovascular Surgery, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan; [x]Department of Cardiology, Kansai Denryoku Hospital, Osaka, Japan; [y]Department of Cardiovascular Surgery, Kokura Memorial Hospital, Kitakyushu, Japan; [z]Department of Cardiovascular Surgery, Shizuoka General Hospital, Shizuoka, Japan; [aa]Department of Cardiovascular Surgery, Shizuoka City Shizuoka Hospital, Shizuoka, Japan; [bb]Department of Cardiovascular Surgery, Osaka Red Cross Hospital, Osaka, Japan; [cc]Department of Cardiovascular Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan; [dd]Department of Cardiology, Shimabara Hospital, Kyoto, Japan; [ee]Department of Cardiology, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan; [ff]Department of Cardiovascular Surgery, Mitsubishi Kyoto Hospital, Kyoto, Japan; [gg]Department of Cardiology, Mitsubishi Kyoto Hospital, Kyoto, Japan; [hh]Department of Cardiology, Shizuoka City Shizuoka Hospital, Shizuoka, Japan; [ii]Department of Cardiology, Osaka Red Cross Hospital, Osaka, Japan; [jj]Department of Cardiovascular Surgery, Kurashiki Central Hospital, Kurashiki, Japan; and the [kk]Department of Cardiovascular Surgery, The Tazuke Kofukai Medical Research Institute, Kitano Hospital, Osaka, Japan.

Manuscript received August 10, 2021; revised manuscript received November 24, 2021, accepted December 12, 2021.

FIGURE 1 **Study Flowchart**



Among the final study population of 39,427 patients, 15,561 patients had diabetes and 23,866 patients did not have diabetes. AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CREDO-Kyoto = Coronary Revascularization Demonstrating Outcome Study in Kyoto; DM = diabetes mellitus; PCI = percutaneous coronary intervention.

(Supplemental Appendix A). We pooled the 3 cohorts with a total of 40,743 patients. From the pooled population, we excluded 1,093 who had undergone combined noncoronary surgery, 207 patients who refused to participate in the registry, and 4 patients in cohort 1 who presented with AMI (violation for the inclusion criteria). After further excluding 12 patients with unknown diabetes status, the final study population consisted of 39,427 patients (15,561 patients with diabetes and 23,866 patients without diabetes) of whom 33,144 patients underwent PCI and 6,283 patients underwent CABG (**Figure 1**). For the subgroup

analysis stratified by the clinical presentation of AMI and non-AMI, we excluded 9,329 patients from cohort 1 and obtained the data set of 30,098 patients (11,909 patients with diabetes and 18,189 patients without diabetes) (Figure 1).

The relevant ethics committees in all the participating centers approved the study protocol. Because enrollment was retrospective, written informed consent from the patients was waived; however, we excluded the 207 patients who refused to participate in the study when contacted for follow-up. This strategy is concordant with the guidelines of the Japanese Ministry of Health, Labor and Welfare.

DEFINITIONS AND OUTCOME MEASURES. The definitions for baseline characteristics were consistent across the 3 cohorts. Patients with diabetes were defined as those receiving treatment with oral hypoglycemic agents or insulin, those with prior clinical diagnosis of diabetes, those with hemoglobin A_{1c} levels of ≥6.5%, and those with nonfasting blood glucose levels of ≥200 mg/dL. Hemoglobin A_{1c} levels were expressed in National Glycohemoglobin Standardization Program percentages. Left ventricular ejection fraction was measured either by left ventriculography or echocardiography. Prior stroke was defined as an ischemic or hemorrhagic stroke with neurological symptoms lasting >24 hours. Peripheral vascular disease was regarded as present when carotid, aortic, or other peripheral vascular diseases were being treated or when affected patients were scheduled for surgical or endovascular interventions. Renal function was expressed as estimated glomerular filtration rate and calculated according to the Modification of Diet in Renal Disease formula modified for Japanese patients.[12] High-intensity statin therapy was defined as atorvastatin doses of ≥ 20 mg, fluvastatin doses of ≥40 mg, pitavastatin doses of ≥4 mg, rosuvastatin doses of ≥10 mg, or simvastatin doses of ≥20 mg.

The primary outcome measure in the present study were major adverse cardiovascular and cerebral endpoints (MACCE), defined as a composite of all-cause death, myocardial infarction (MI), and stroke. We also assessed a respective endpoint of all-cause death, cardiovascular death, noncardiovascular death, MI, stroke, target vessel revascularization (TVR), any coronary revascularization, and heart failure hospitalization. The definitions for outcome measures were consistent across the 3 cohorts. Death was regarded as cardiac in origin, unless obvious noncardiac causes could be identified; thus, death from an unknown cause and any death during the index hospitalization for coronary revascularization were regarded as cardiac death. Cardiovascular death included cardiac death and other death related to stroke, renal disease, and vascular disease. MI was adjudicated according to the ARTS (Arterial Revascularization Therapies Study) definition in which only Q-wave MI was regarded as myocardial infarction

TABLE 1 Baseline Characteristics: Diabetes Versus Nondiabetes

	Diabetes (n = 15,561)	Nondiabetes (n = 23,866)	*P* Value
Clinical characteristics			
Age, y	67.9 ± 10.0	68.8 ± 11.2	<0.001
Age, tertiles[a]			<0.001
≤64 y	5,419 (34.8)	7,835 (32.8)	
64-73 y	5,377 (34.6)	7,194 (30.1)	
>73 y	4,765 (30.6)	8,837 (37.0)	
Men[a]	11,163 (71.7)	17,387 (72.9)	0.02
Body mass index, kg/m^2	24.1 ± 3.6	23.5 ± 3.4	<0.001
Body mass index ≥25.0 kg/m^2[a]	5,451 (35.7)	7,010 (30.1)	<0.001
Acute myocardial infarction[a]	3,579 (23.0)	6,823 (28.6)	<0.001
ST-segment elevation myocardial infarction	2,791 (17.9)	5,521 (23.1)	<0.001
Hypertension[a]	12,666 (81.4)	18,548 (77.7)	<0.001
Hemoglobin A_{1c}, %	7.5 ± 1.5	5.7 ± 0.4	<0.001
Diabetes mellitus on oral antidiabetes	9,501 (61.1)	0 (0)	
Diabetes mellitus on insulin therapy	3,519 (22.7)	0 (0)	
Current smoking[a]	4,331 (28.0)	6,903 (29.1)	0.02
eGFR, mL/min/1.73 m^2	62.9 ± 28.8	66.1 ± 26.2	<0.001
eGFR <30 mL/min/1.73 m^2 without dialysis[a]	952 (6.1)	831 (3.5)	<0.001
Dialysis[a]	1,027 (6.6)	684 (2.9)	<0.001
Heart failure[a,b]	3,045 (19.6)	3,748 (15.7)	<0.001
Left ventricular ejection fraction, %	58.2 ± 13.9	60.0 ± 13.0	<0.001
Left ventricular ejection fraction ≤40%	1,597 (10.3)	1,745 (7.3)	<0.001
Mitral regurgitation grade ≥3/4	663 (5.1)	1,007 (5.1)	1.00
Prior myocardial infarction[a]	2,712 (17.4)	3,284 (13.8)	<0.001
Prior stroke[a]	2,308 (14.8)	2,772 (11.6)	<0.001
Peripheral vascular disease[a]	1,701 (10.9)	1,971 (8.3)	<0.001
Atrial fibrillation[a]	1,328 (8.5)	2,175 (9.1)	0.0503
Anemia (hemoglobin <11.0 g/dL)[a]	2,493 (16.0)	2,608 (10.9)	<0.001
Chronic obstructive pulmonary disease[a]	434 (2.8)	922 (3.9)	<0.001
Liver cirrhosis[a]	508 (3.3)	590 (2.5)	<0.001
Malignancy[a]	1,571 (10.1)	2,345 (9.8)	0.39
Procedural characteristics			
Number of target lesions or anastomoses	1.8 ± 1.1	1.6 ± 0.9	<0.001
Target of left main coronary artery	1,500 (9.6)	1,966 (8.2)	<0.001
Target of proximal LAD	9,756 (67.7)	14,281 (63.4)	<0.001
Target of chronic total occlusion	2,988 (20.7)	3,835 (17.0)	<0.001
Multivessel disease	10,808 (69.5)	13,322 (55.8)	<0.001
Percutaneous coronary intervention	12,481 (80.2)	20,663 (86.6)	<0.001
Total number of stents	1.8 ± 1.4	1.6 ± 1.2	<0.001
Total stent length, mm	41.5 ± 32.3	36.0 ± 28.0	<0.001
Stent use	11,531 (92.4)	18,926 (91.6)	0.01
Drug-eluting stent use	6,924 (60.0)	10,198 (53.9)	<0.001
New-generation drug-eluting stent use	4,048 (35.1)	6,135 (32.4)	<0.001
Coronary artery bypass graft	3,080 (19.8)	3,203 (13.4)	<0.001
Internal thoracic artery use	2,970 (96.4)	3,031 (94.6)	<0.001
Off-pump surgery	1,428 (46.4)	1,463 (45.7)	0.61

Continued on the next page

TABLE 1 Continued

	Diabetes (n = 15,561)	Nondiabetes (n = 23,866)	*P* Value
Baseline medications			
Aspirin	14,946 (96.1)	22,944 (96.2)	0.71
$P2Y_{12}$ receptor blockers	12,075 (77.6)	19,624 (82.3)	<0.001
Cilostazol	1,544 (9.9)	2,347 (9.8)	0.79
Statins	8,411 (54.1)	12,833 (53.8)	0.58
High intensity statins[c]	215 (1.4)	303 (1.3)	0.36
Beta-blockers	4,860 (31.3)	7,304 (30.6)	0.19
ACE inhibitors or angiotensin receptor blockers	8,367 (53.8)	12,015 (50.4)	<0.001
Nitrates	5,395 (34.7)	8,677 (36.4)	<0.001
Calcium channel blockers	7,269 (46.7)	10,435 (43.7)	<0.001
Nicorandil	3,606 (23.2)	4,972 (20.8)	<0.001
Oral anticoagulants	2,166 (13.9)	2,966 (12.4)	<0.001
Warfarin	2,089 (13.4)	2,850 (11.9)	<0.001
Nonvitamin K antagonist oral anticoagulants	79 (0.5)	116 (0.5)	0.82

Values are mean ± SD or n (%). Values were missing for body mass index in 832 patients, for hemoglobin A_{1c} in 10,716 patients, for diabetes mellitus on insulin therapy in 64 patients, for current smoking in 177 patients, for eGFR in 510 patients, for heart failure in 26 patients, for left ventricular ejection fraction in 6,129 patients, for mitral regurgitation in 6,920 patients, for prior myocardial infarction in 15 patients, for prior stroke in 8 patients, for peripheral vascular disease in 8 patients, for atrial fibrillation in 5 patients, for chronic obstructive pulmonary disease in 5 patients, for liver cirrhosis in 12 patients, for malignancy in 6 patients, for baseline medications in 23 patients, and for high-intensity statins in 38 patients. [a]Risk-adjusting variables selected for the Cox proportional hazard models. [b]Heart failure included both prior and current heart failure. [c]High-intensity statin therapy was defined as atorvastatin doses of ≥20 mg, fluvastatin doses of ≥40 mg, pitavastatin doses of ≥4 mg, rosuvastatin doses of ≥10 mg, or simvastatin doses of ≥20 mg.

ACE = angiotensin converting enzyme; eGFR = estimated glomerular filtration rate; LAD = left anterior descending coronary artery.

when it occurred within 7 days of the index procedure.[13] Stroke was defined as an ischemic or hemorrhagic stroke with neurological symptoms lasting >24 hours. TVR was defined as either PCI or CABG performed for restenosis, thrombosis, de novo disease progression of the target vessel, or graft failure. Any coronary revascularization was defined as either PCI or CABG for any reasons. Heart failure hospitalization was defined as hospitalization for worsening heart failure requiring intravenous drug therapy.

DATA COLLECTION FOR BASELINE CHARACTERISTICS AND FOLLOW-UP EVENTS. Clinical, angiographic, and procedural data were collected from the hospital charts or hospital databases according to the prespecified definitions by experienced clinical research coordinators from the Research Institute for Production Development (Kyoto, Japan) (Supplemental Appendix B). Follow-up data were collected from the hospital charts or obtained through contact with patients, their relatives, or the referring physicians. Clinical events after the index procedure were assessed as follow-up events, except for scheduled staged coronary revascularization procedures performed within 3 months of the index procedure, which were regarded as part of the index procedure. The clinical event committee determined whether any incidents were clinical events (Supplemental Appendix C).

STATISTICAL ANALYSIS. Data for categorical variables were calculated as numbers and percentages and were compared using chi-square test with Yates' continuity correction. Data for continuous variables were expressed as mean ± SD or as median (IQR) and were compared using Student's *t*-test or the Wilcoxon rank-sum test. HRs and their 95% CIs were calculated using univariate or multivariable Cox proportional hazard models to estimate the risk of diabetes relative to nondiabetes on the clinical outcome measures. Clinically relevant variables listed in **Table 1** were simultaneously included in the multivariable models as the explanatory variables to adjust for the baseline characteristics. The enrollment periods of cohorts 1, 2, and 3 were also included as a stratification variable to fit separate baseline hazard functions. We explored the 4 potential modifiers of the risk of diabetes relative to nondiabetes for clinical outcome measures in the subgroup analyses (age tertiles, sex, mode of revascularization of PCI or CABG, and clinical presentation of AMI or non-AMI). The potential risk modifiers were arbitrarily selected based on clinical relevance. In the subgroup analyses, we added the interaction variables in the multivariable models. We calculated a type III sum of squares to estimate the effect of interactions. Because we did not enroll patients with AMI in cohort 1, we excluded those who were included in cohort 1 from subgroup analysis of clinical presentation of AMI or non-AMI. To confirm the interaction between diabetes status and mode of revascularization in patients with complex coronary artery disease, the subgroup analysis for the mode of revascularization was also conducted in patients with complex coronary artery disease (defined as either multivessel disease or left main coronary artery disease) as a sensitivity analysis. As another sensitivity analysis, we stratified the patients according to the enrollment periods of cohorts 1, 2, and 3. The explanatory variable of AMI was removed in the models for patients enrolled in cohort 1.

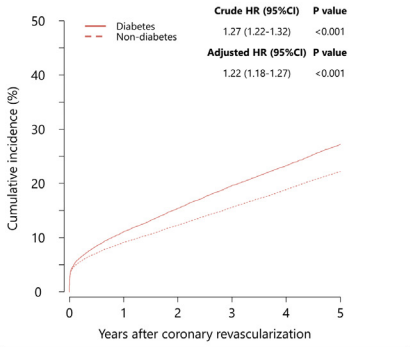
Two-sided *P* values of <0.05 indicated statistical significance. We used the R statistical software (version 4.0.2, R Foundation for Statistical Computing) to analyze all the data.

RESULTS

BASELINE CHARACTERISTICS. In comparison with patients without diabetes, patients with diabetes were younger (age 67.9 ± 10.0 years vs 68.8 ± 11.2 years; $P < 0.001$), less likely to be men (71.9% vs 72.9%; $P = 0.02$), and less often presented with AMI

FIGURE 2 Kaplan-Meier Curves for the Clinical Outcome Measures: Diabetes Versus Nondiabetes

A Major adverse cardiovascular and cerebral endpoints

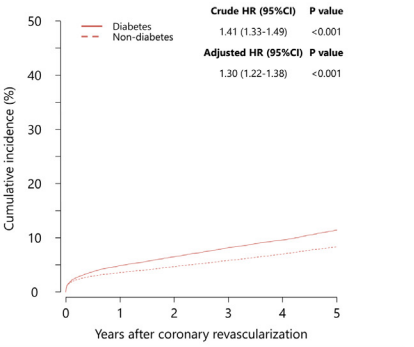


	0	1 year	3 years	5 years	
Diabetes	0	1710	2986	4044	N of patients with events
	0%	11.1%	19.6%	27.3%	Cumulative incidence
	15561	13503	11816	8584	N of patients at risk
Non-diabetes	0	2160	3657	5066	N of patients with events
	0%	9.1%	15.6%	22.2%	Cumulative incidence
	23866	21283	19194	14184	N of patients at risk

B All-cause death

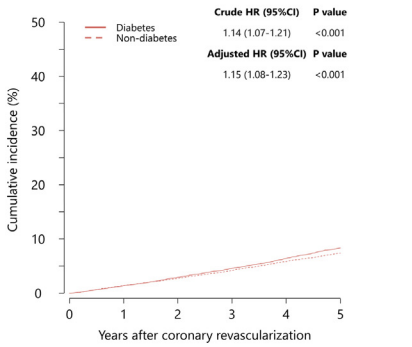
	0	1 year	3 years	5 years	
Diabetes	0	949	1881	2768	N of patients with events
	0%	6.2%	12.4%	18.8%	Cumulative incidence
	15561	14245	12857	9550	N of patients at risk
Non-diabetes	0	1168	2285	3420	N of patients with events
	0%	4.9%	9.8%	15.1%	Cumulative incidence
	23866	22253	20492	15421	N of patients at risk

C Cardiovascular death



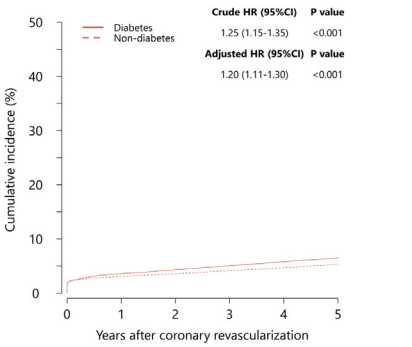
	0	1 year	3 years	5 years	
Diabetes	0	748	1228	1644	N of patients with events
	0%	4.9%	8.2%	11.4%	Cumulative incidence
	15561	14245	12857	9550	N of patients at risk
Non-diabetes	0	845	1350	1851	N of patients with events
	0%	3.6%	5.8%	8.3%	Cumulative incidence
	23866	22253	20492	15421	N of patients at risk

D Noncardiovascular death



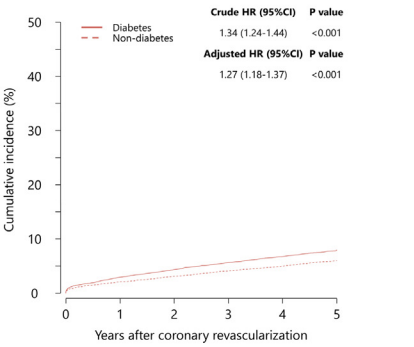
	0	1 year	3 years	5 years	
Diabetes	0	201	653	1124	N of patients with events
	0%	1.4%	4.6%	8.4%	Cumulative incidence
	15561	14245	12857	9550	N of patients at risk
Non-diabetes	0	323	935	1569	N of patients with events
	0%	1.4%	4.2%	7.4%	Cumulative incidence
	23866	22253	20492	15421	N of patients at risk

E Myocardial infarction



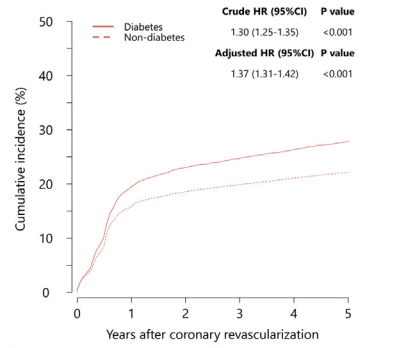
	0	1 year	3 years	5 years	
Diabetes	0	550	750	921	N of patients with events
	0%	3.6%	5.1%	6.5%	Cumulative incidence
	15561	13795	12301	9062	N of patients at risk
Non-diabetes	0	729	959	1174	N of patients with events
	0%	3.1%	4.2%	5.3%	Cumulative incidence
	23866	21624	19754	14754	N of patients at risk

F Stroke



	0	1 year	3 years	5 years	
Diabetes	0	441	812	1083	N of patients with events
	0%	2.9%	5.6%	7.9%	Cumulative incidence
	15561	13938	12327	9016	N of patients at risk
Non-diabetes	0	484	920	1273	N of patients with events
	0%	2.1%	4.1%	6.0%	Cumulative incidence
	23866	21885	19878	14779	N of patients at risk

G Target vessel revascularization

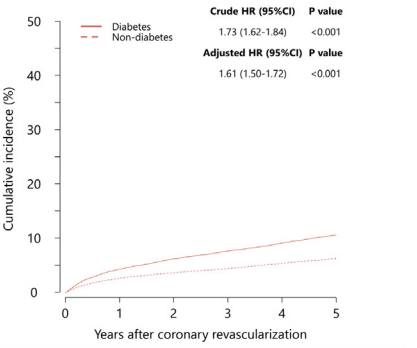


	0	1 year	3 years	5 years	
Diabetes	0	2879	3598	3963	N of patients with events
	0%	19.5%	24.8%	27.9%	Cumulative incidence
	15561	11473	9637	6831	N of patients at risk
Non-diabetes	0	3637	4497	4924	N of patients with events
	0%	15.9%	19.9%	22.1%	Cumulative incidence
	23866	18716	16385	11999	N of patients at risk

H Any coronary revascularization

	0	1 year	3 years	5 years	
Diabetes	0	3456	4414	4920	N of patients with events
	0%	23.4%	30.4%	34.7%	Cumulative incidence
	15561	10922	8913	6217	N of patients at risk
Non-diabetes	0	4410	5619	6231	N of patients with events
	0%	19.3%	24.9%	28.1%	Cumulative incidence
	23866	17969	15367	11122	N of patients at risk

I Heart failure hospitalization



	0	1 year	3 years	5 years	
Diabetes	0	632	1094	1451	N of patients with events
	0%	4.3%	7.6%	10.6%	Cumulative incidence
	15561	13726	12112	8870	N of patients at risk
Non-diabetes	0	588	977	1333	N of patients with events
	0%	2.6%	4.4%	6.2%	Cumulative incidence
	23866	21782	19864	14819	N of patients at risk

Continued on the next page

(23.0% vs 28.6%; $P < 0.001$). Patients with diabetes more often had comorbidities such as hypertension (81.4% vs 77.7%; $P < 0.001$), chronic renal failure (estimated glomerular filtration rate of <30 mL/min/1.73 m^2 without dialysis: 6.1% vs 3.5%; dialysis: 6.6% vs 2.9%; $P < 0.001$), heart failure (19.6% vs 15.7%; $P < 0.001$), and anemia (16.0% vs 10.9%; $P < 0.001$). The previous history of cardiovascular events such as MI (17.4% vs 13.8%; $P < 0.001$) and stroke (14.8% vs 11.6%; $P < 0.001$) were more prevalent in patients with diabetes than in those without diabetes (**Table 1**). Regarding procedural characteristics, multivessel disease was present in 69.5% of patients with diabetes and in 55.8% of patients without diabetes ($P < 0.001$). PCI was performed in 80.2% of patients with diabetes and in 86.6% of patients without diabetes ($P < 0.001$). Among 33,144 patients who underwent PCI, 6,335 patients (19.1%) underwent staged PCI within 3 months after the index procedure.

Baseline characteristics were substantially different according to age tertiles, sex, mode of revascularization, and clinical presentation, whereas the differences between patients with versus without diabetes in each subgroup were mostly consistent with those in the entire study population (Supplemental Tables 1 to 4). Younger patients were more likely to be men and had greater body mass index. Current smoking habit was present in 45.5% of patients ≤64 years of age, but only in 15.2% of patients >73 years of age. Older patients more often had the previous history of stroke and had comorbidities such as peripheral vascular disease, atrial fibrillation, anemia, and malignancy. Men, compared with women, less often had anemia and renal failure without dialysis and more often had current smoking habits. Regarding mode of revascularization, patients who underwent PCI more often had AMI presentation, heart failure, and malignancy and less often had prior MI, prior stroke, peripheral vascular disease, and anemia than those who underwent CABG (Supplemental Tables 1 to 4).

Complex coronary artery disease was present in 25,005 patients. Patients with complex coronary artery disease less often presented with AMI, but they were older and more often had comorbidities such as hypertension, diabetes, heart failure, prior MI, prior stroke, and peripheral vascular disease. The vast majority of patients without complex coronary artery disease underwent PCI (Supplemental Table 5).

Baseline characteristics were substantially different across the 3 cohorts. Patients in cohort 3 compared with those in cohort 1 were older and more often had comorbidities such as hypertension, heart failure, mitral regurgitation, and malignancy, but less often had prior histories of MI and stroke (Supplemental Table 6).

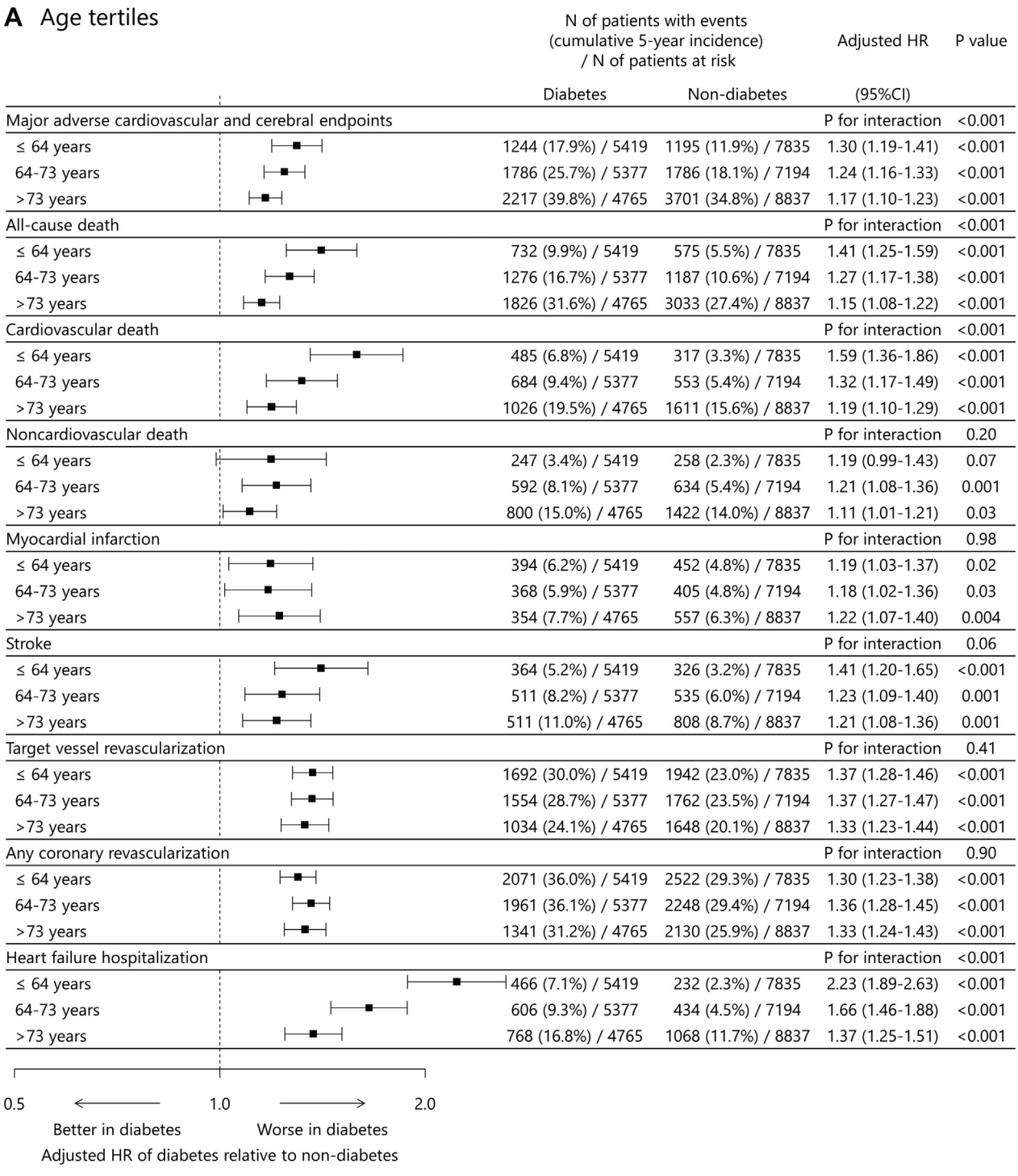
CLINICAL OUTCOMES IN THE ENTIRE STUDY POPULATION. Median follow-up duration was 5.6 (IQR: 4.4-6.9) years in the entire study population; 10.6 (IQR: 5.0-11.8) years in cohort 1, 5.1 (IQR: 4.2-5.9) years in cohort 2, and 5.7 (IQR: 4.4-6.7) years in cohort 3. Clinical follow-up information was obtained in 97.9% of patients (cohort 1: 98.8%, cohort 2: 98.4%, and cohort 3: 96.9%) at 1 year, 95.2% (cohort 1: 94.7%, cohort 2: 96.3%, and cohort 3: 94.2%) at 3 years, and 79.1% (cohort 1: 88.1%, cohort 2: 70.0%, and cohort 3: 82.7%) at 5 years after the index procedure. Diabetes as compared with nondiabetes was associated with significantly higher crude and adjusted risk for all the outcome measures. The magnitude of excess adjusted mortality risk of diabetes relative to nondiabetes was modest, which was mainly driven by the excess risk for cardiovascular death. Nevertheless, diabetes, compared with nondiabetes, also had significant excess risk for noncardiovascular death. The magnitude of excess adjusted risk of diabetes relative to nondiabetes was moderate for heart failure hospitalization, while it was modest for MI, stroke, TVR, and any coronary revascularization (**Figure 2**).

SUBGROUP ANALYSES STRATIFIED BY THE MODIFIERS FOR THE RISK OF DIABETES. With regard to primary outcome measure of MACCE, there was a significant interaction between adjusted risk of diabetes relative to nondiabetes and age tertiles, while no significant interaction was observed between diabetes status and other subgroups such as sex, mode of revascularization, and clinical presentation of AMI. The magnitude of the excess risk of diabetes relative to nondiabetes increased in younger patients for MACCE (**Figure 3**, Supplemental Figure 1).

FIGURE 2 Continued

Kaplan-Meier curves for **(A)** major adverse cardiovascular and cerebral endpoints, **(B)** all-cause death, **(C)** cardiovascular death, **(D)** noncardiovascular death, **(E)** myocardial infarction, **(F)** stroke, **(G)** target vessel revascularization, **(H)** any coronary revascularization, and **(I)** heart failure hospitalization. The Kaplan-Meier curves were truncated at 5 years.

FIGURE 3 **Forest Plots for the Adjusted HRs of Diabetes**

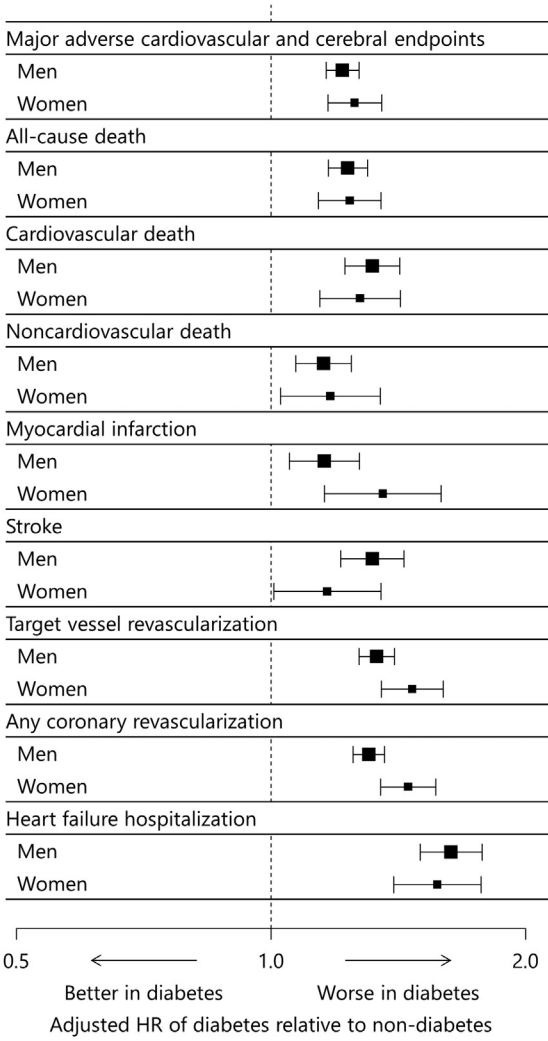


Forest plots for **(A)** age tertiles, **(B)** sex, **(C)** mode of revascularization, and **(D)** clinical presentation. Cumulative incidence was represented by the values at 5 years. Number of patients with event and the HRs were estimated through the entire follow-up period. To calculate HRs and interactions, we incorporated the risk-adjusting variables listed in Table 1. Abbreviations as in Figure 1.

Continued on the next page

FIGURE 3 Continued

B Sex



	N of patients with events (cumulative 5-year incidence) / N of patients at risk		Adjusted HR	P value
	Diabetes	Non-diabetes	(95%CI)	
Major adverse cardiovascular and cerebral endpoints			P for interaction	0.54
Men	3712 (26.9%) / 11163	4874 (21.9%) / 17387	1.21 (1.16-1.27)	<0.001
Women	1535 (28.2%) / 4398	1808 (22.8%) / 6479	1.26 (1.17-1.35)	<0.001
All-cause death			P for interaction	0.96
Men	2685 (18.4%) / 11163	3447 (14.8%) / 17387	1.23 (1.17-1.30)	<0.001
Women	1149 (19.9%) / 4398	1348 (16.0%) / 6479	1.24 (1.14-1.35)	<0.001
Cardiovascular death			P for interaction	0.40
Men	1465 (10.6%) / 11163	1678 (7.7%) / 17387	1.32 (1.22-1.42)	<0.001
Women	730 (13.5%) / 4398	803 (10.1%) / 6479	1.27 (1.14-1.42)	<0.001
Noncardiovascular death			P for interaction	0.83
Men	1220 (8.7%) / 11163	1769 (7.7%) / 17387	1.15 (1.07-1.24)	<0.001
Women	419 (7.4%) / 4398	545 (6.6%) / 6479	1.18 (1.03-1.35)	0.02
Myocardial infarction			P for interaction	0.13
Men	790 (6.4%) / 11163	1062 (5.4%) / 17387	1.16 (1.05-1.27)	0.003
Women	326 (6.8%) / 4398	352 (5.1%) / 6479	1.36 (1.16-1.59)	<0.001
Stroke			P for interaction	0.08
Men	1022 (8.0%) / 11163	1215 (5.8%) / 17387	1.32 (1.21-1.44)	<0.001
Women	364 (7.7%) / 4398	454 (6.3%) / 6479	1.17 (1.01-1.35)	0.04
Target vessel revascularization			P for interaction	0.02
Men	3164 (28.6%) / 11163	4114 (23.2%) / 17387	1.33 (1.27-1.40)	<0.001
Women	1116 (26.0%) / 4398	1238 (19.2%) / 6479	1.47 (1.35-1.60)	<0.001
Any coronary revascularization			P for interaction	0.003
Men	3964 (35.5%) / 11163	5295 (29.5%) / 17387	1.31 (1.25-1.36)	<0.001
Women	1409 (32.6%) / 4398	1605 (24.5%) / 6479	1.45 (1.35-1.57)	<0.001
Heart failure hospitalization			P for interaction	0.37
Men	1200 (9.4%) / 11163	1152 (5.6%) / 17387	1.63 (1.50-1.78)	<0.001
Women	640 (13.6%) / 4398	582 (7.8%) / 6479	1.57 (1.40-1.77)	<0.001

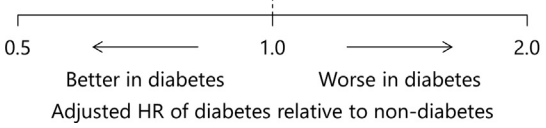
As for respective outcome measures, there was a significant interaction between age tertiles and the adjusted risk of diabetes relative to nondiabetes for all-cause death, cardiovascular death, and heart failure hospitalization. In terms of TVR and any coronary revascularization, there was a significant diabetes-by-subgroup interaction in the sex and mode of revascularization subgroups (**Figure 3,** Supplemental Figures 2 and 3). The magnitude of the excess risk of diabetes relative to nondiabetes for these outcome measures was greater in women and in those who underwent PCI. Regarding clinical presentation, there was no significant diabetes-by-subgroup interaction in the AMI/non-AMI subgroups for MACCE and respective outcome measures. There was a consistent trend toward higher risk of diabetes relative to nondiabetes for all the outcome measures regardless of clinical presentation of AMI except for noncardiovascular death in patients who presented with AMI (**Figure 3,** Supplemental Figure 4).

In the sensitivity analysis in patients who had a complex coronary artery disease, the results in the subgroup analysis stratified by mode of revascularization were consistent with those in the main results

FIGURE 3 Continued

C Mode of revascularization

	N of patients with events (cumulative 5-year incidence) / N of patients at risk		Adjusted HR	P value
	Diabetes	Non-diabetes	(95%CI)	
Major adverse cardiovascular and cerebral endpoints			P for interaction	0.13
PCI	4125 (27.4%) / 12481	5682 (22.2%) / 20663	1.23 (1.18-1.29)	<0.001
CABG	1122 (26.6%) / 3080	1000 (22.2%) / 3203	1.18 (1.08-1.29)	<0.001
All-cause death			P for interaction	0.22
PCI	2982 (18.8%) / 12481	4051 (15.1%) / 20663	1.24 (1.18-1.31)	<0.001
CABG	852 (18.9%) / 3080	744 (14.8%) / 3203	1.20 (1.09-1.33)	<0.001
Cardiovascular death			P for interaction	0.38
PCI	1684 (11.3%) / 12481	2082 (8.2%) / 20663	1.31 (1.23-1.41)	<0.001
CABG	511 (11.8%) / 3080	399 (9.0%) / 3203	1.27 (1.11-1.46)	<0.001
Noncardiovascular death			P for interaction	0.30
PCI	1298 (8.5%) / 12481	1969 (7.5%) / 20663	1.16 (1.08-1.25)	<0.001
CABG	341 (8.0%) / 3080	345 (6.4%) / 3203	1.12 (0.96-1.31)	0.14
Myocardial infarction			P for interaction	0.03
PCI	940 (6.9%) / 12481	1231 (5.3%) / 20663	1.24 (1.13-1.35)	<0.001
CABG	176 (4.9%) / 3080	183 (5.3%) / 3203	1.00 (0.81-1.24)	0.98
Stroke			P for interaction	0.69
PCI	1048 (7.7%) / 12481	1376 (5.7%) / 20663	1.27 (1.16-1.38)	<0.001
CABG	338 (8.6%) / 3080	293 (7.4%) / 3203	1.27 (1.09-1.50)	0.003
Target vessel revascularization			P for interaction	0.001
PCI	3905 (32.0%) / 12481	4978 (23.9%) / 20663	1.39 (1.33-1.45)	<0.001
CABG	375 (10.9%) / 3080	374 (10.5%) / 3203	1.07 (0.92-1.24)	0.37
Any coronary revascularization			P for interaction	<0.001
PCI	4909 (39.9%) / 12481	6422 (30.5%) / 20663	1.37 (1.32-1.42)	<0.001
CABG	464 (13.5%) / 3080	478 (13.1%) / 3203	1.04 (0.92-1.19)	0.51
Heart failure hospitalization			P for interaction	0.63
PCI	1450 (10.7%) / 12481	1483 (6.3%) / 20663	1.61 (1.49-1.74)	<0.001
CABG	390 (10.2%) / 3080	251 (5.6%) / 3203	1.61 (1.37-1.90)	<0.001



(Supplemental Figure 5). The results of the sensitivity analysis in cohorts 1, 2, and 3, separately, were largely in line with those observed in the entire study population (Supplemental Figures 6 to 8).

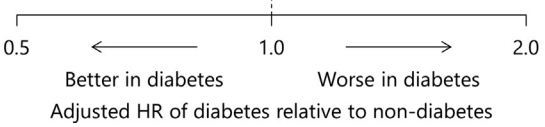
DISCUSSION

Diabetes compared with nondiabetes was independently associated with worse cardiovascular outcomes up to 5 years after coronary revascularization in our large-scale pooled registry including 15,561 patients with diabetes and 23,866 patients without diabetes. We found a few modifiers of the excess risk of diabetes relative to nondiabetes for clinical outcome measures. In terms of primary endpoint of MACCE, there was a significant interaction between diabetes status and age tertiles, while no significant interaction was observed between diabetes status and sex, mode of revascularization, or clinical presentation of AMI (**Central Illustration**). The excess adjusted risk of diabetes relative to nondiabetes for all-cause death varied widely from a 41% increase in younger patients to a 15% increase in older patients. Our findings of the greater excess mortality risk in younger patients with diabetes were largely consistent with those observed in the general

FIGURE 3 Continued

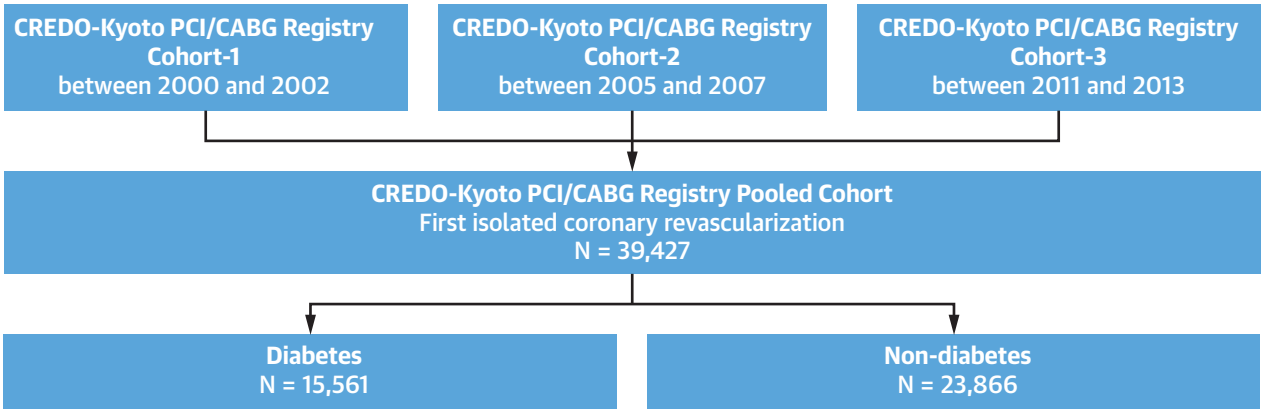
D Clinical presentation

	N of patients with events (cumulative 5-year incidence) / N of patients at risk		Adjusted HR	P value
	Diabetes	Non-diabetes	(95%CI)	
Major adverse cardiovascular and cerebral endpoints			P for interaction	0.83
AMI	1166 (30.7%) / 3579	1913 (26.0%) / 6823	1.16 (1.07-1.25)	<0.001
Non-AMI	2421 (26.4%) / 8330	2733 (21.6%) / 11366	1.20 (1.13-1.27)	<0.001
All-cause death			P for interaction	0.35
AMI	879 (22.9%) / 3579	1437 (19.4%) / 6823	1.16 (1.06-1.27)	0.001
Non-AMI	1691 (17.9%) / 8330	1815 (14.1%) / 11366	1.24 (1.15-1.33)	<0.001
Cardiovascular death			P for interaction	0.46
AMI	584 (16.1%) / 3579	859 (12.1%) / 6823	1.24 (1.10-1.39)	<0.001
Non-AMI	898 (9.9%) / 8330	835 (6.7%) / 11366	1.31 (1.18-1.44)	<0.001
Noncardiovascular death			P for interaction	0.13
AMI	295 (8.1%) / 3579	578 (8.2%) / 6823	1.02 (0.88-1.19)	0.75
Non-AMI	793 (8.9%) / 8330	980 (7.9%) / 11366	1.17 (1.06-1.29)	0.001
Myocardial infarction			P for interaction	0.29
AMI	225 (6.7%) / 3579	358 (5.3%) / 6823	1.18 (1.00-1.41)	0.06
Non-AMI	575 (6.8%) / 8330	702 (6.0%) / 11366	1.10 (0.98-1.23)	0.11
Stroke			P for interaction	0.42
AMI	278 (8.2%) / 3579	397 (5.9%) / 6823	1.33 (1.13-1.56)	<0.001
Non-AMI	632 (7.5%) / 8330	691 (5.7%) / 11366	1.24 (1.11-1.38)	<0.001
Target vessel revascularization			P for interaction	0.17
AMI	901 (28.3%) / 3579	1421 (22.5%) / 6823	1.25 (1.15-1.37)	<0.001
Non-AMI	1920 (23.6%) / 8330	2008 (17.8%) / 11366	1.40 (1.32-1.50)	<0.001
Any coronary revascularization			P for interaction	0.53
AMI	1182 (37.2%) / 3579	1879 (29.7%) / 6823	1.27 (1.17-1.36)	<0.001
Non-AMI	2578 (31.7%) / 8330	2824 (25.1%) / 11366	1.35 (1.28-1.43)	<0.001
Heart failure hospitalization			P for interaction	0.27
AMI	376 (11.3%) / 3579	489 (7.4%) / 6823	1.48 (1.29-1.71)	<0.001
Non-AMI	930 (11.3%) / 8330	783 (6.5%) / 11366	1.57 (1.42-1.73)	<0.001

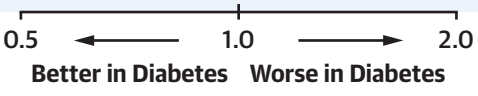


population.[2-4,14,15] However, the absolute mortality risk in the younger patients with diabetes were extremely low in the general population, whereas in the present study, the observed absolute difference in all-cause death between diabetes and nondiabetes in the younger tertile was substantial (9.9% vs 5.5% at 5 years after coronary revascularization). The observed interaction between age tertiles and the effect of diabetes status on all-cause death was driven mainly by the higher excess risk of cardiovascular death in younger patients with diabetes. Moreover, we might assume the higher excess mortality risk of diabetes relative to nondiabetes among younger patients might be related to the higher excess risk for heart failure hospitalization. More aggressive interventions for secondary prevention in patients with diabetes might be particularly relevant in a patient population with greater excess mortality risk of diabetes relative to nondiabetes. Our results might suggest that more aggressive interventions for secondary prevention including liberal use of sodium-glucose cotransporter-2 inhibitors with a specific effect for heart failure[16-18] might reduce the mortality risk in younger patients who underwent coronary revascularization. Alternatively, therapeutic interventions for secondary prevention in patients with diabetes might be

CENTRAL ILLUSTRATION **Study Flowchart and Forest Plots for the Adjusted HRs of Diabetes**



Adjusted HR of Diabetes Relative to Non-Diabetes for Major Adverse Cardiovascular and Cerebral Endpoints	N of Patients With Major Adverse Cardiovascular and Cerebral Endpoints (Cumulative 5-Year Incidence) / N of Patients at Risk		Adjusted HR (95% CI)	*P* Value
	Diabetes	Non-Diabetes		
Age tertiles			*P* for interaction	< 0.001
≤64 years	1,244 (17.9%) / 5,419	1,195 (11.9%) / 7,835	1.30 (1.19-1.41)	< 0.001
64-73 years	1,786 (25.7%) / 5,377	1,786 (18.1%) / 7,194	1.24 (1.16-1.33)	< 0.001
>73 years	2,217 (39.8%) / 4,765	3,701 (34.8%) / 8,837	1.17 (1.10-1.23)	< 0.001
Sex			*P* for interaction	0.54
Men	3,712 (26.9%) / 11,163	4,874 (21.9%) / 17,387	1.21 (1.16-1.27)	< 0.001
Women	1,535 (28.2%) / 4,398	1,808 (22.8%) / 6,479	1.26 (1.17-1.35)	< 0.001
Mode of revascularization			*P* for interaction	0.13
PCI	4,125 (27.4%) / 12,481	5,682 (22.2%) / 20,663	1.23 (1.18-1.29)	< 0.001
CABG	1,122 (26.6%) / 3,080	1,000 (22.2%) / 3,203	1.18 (1.08-1.29)	< 0.001
Clinical presentation			*P* for interaction	0.83
AMI	1,166 (30.7%) / 3,579	1,913 (26.0%) / 6,823	1.16 (1.07-1.25)	< 0.001
Non-AMI	2,421 (26.4%) / 8,330	2,733 (21.6%) / 11,366	1.20 (1.13-1.27)	< 0.001



Major adverse cardiovascular and cerebral endpoints was defined as a composite of all-cause death, myocardial infarction, and stroke.

Yamaji K, et al. JACC: Asia. 2022;2(3):294-308.

From the pooled CREDO-Kyoto PCI/CABG (Coronary Revascularization Demonstrating Outcome Study in Kyoto Percutaneous Coronary Intervention/Coronary Artery Bypass Graft) registry, we found the excess risk of diabetes relative to nondiabetes for major adverse cardiovascular and cerebral endpoints MACCE was profound in the younger population, whereas no significant interaction was observed between adjusted risk of diabetes relative to nondiabetes for MACCE and other subgroups such as sex, mode of revascularization, and clinical presentation of acute myocardial infarction.

attenuated in older patients with smaller excess mortality risk of diabetes relative to nondiabetes.

The higher risk of diabetes relative to nondiabetes in women has been underscored in the patient-level pooled analysis including 10,448 women who underwent PCI with drug-eluting stents in 26 randomized controlled trials (RCTs), in which 3-year adjusted risks for all-cause death, MI, target lesion revascularization, and definite or probable stent thrombosis in women with diabetes were significantly higher compared with in women without diabetes.[19] Despite the lower absolute risks of cardiovascular events in women, the excess risks of diabetes relative to nondiabetes for cardiovascular events were greater in women than in men in the general population.[20] In line with these studies, women, compared with men, were associated with greater excess risks of diabetes relative to nondiabetes for TVR and any coronary revascularization in our study. In contrast, in the prespecified subgroup analysis of patient-level pooled analysis including 32,877 patients undergoing PCI in 23 RCTs, no significant interaction between sex and clinical outcomes based on diabetes status was observed for 5-year risk of ischemia-driven target lesion revascularization (men vs women; diabetes: 12.6% vs 13.5%; nondiabetes: 9.5% vs 9.7%; $P_{\text{interaction}} = 0.70$).[21] This discrepancy could at least in part be explained by the difference in the lesion complexity between our all-comers registry and RCTs (eg, mean number of treated lesions: 1.7 vs 1.3 lesions); however, further studies are needed to clarify the sex difference in the effect of diabetes on clinical outcomes after coronary revascularization.

Dedicated RCTs have shown that CABG is more beneficial than PCI in patients with diabetes.[22,23] However, no clear interactions between diabetes status and effects of mode of revascularization on long-term clinical outcomes were reported in the recent RCTs.[24-27] According to the collaborative analysis of 11 RCTs, the rate of 5-year mortality among patients with diabetes was significantly higher in the PCI arm than in the CABG arm (HR: 1.44; 95% CI: 1.20-1.74; $P < 0.001$), whereas no significant difference was observed between PCI and CABG among patients without diabetes (HR: 1.02; 95% CI: 0.86-1.21; $P = 0.81$, $P_{\text{interaction}} = 0.008$).[28] The intention of the collaborative analysis was not to explore difference in the magnitude of excess risk of diabetes relative to nondiabetes by mode of revascularization; nevertheless, we could infer that the magnitude of excess mortality risk of diabetes relative to nondiabetes was greater among patients who underwent PCI than in those who underwent CABG. However, in the present study, there was no significant interaction between mode of revascularization (PCI/CABG) and mortality risk of diabetes relative to nondiabetes. This discrepancy might be explained, at least in part, by the older population in our registry (mean patient's age: 68.4 years) compared with the collaborative analysis of RCTs (mean patient's age: 63.6 years), because survival benefit with CABG over PCI in patients with diabetes was profound in younger patients.[29] Meanwhile, there was significant interaction between mode of revascularization and risks of diabetes relative to nondiabetes for coronary events such as MI, TVR, and any coronary revascularization. In patients who underwent CABG, there was virtually no excess risk of diabetes relative to nondiabetes for coronary events. Our results not only support the benefit of CABG in relation to PCI in patients with diabetes, but also highlight the need for more aggressive secondary prevention measures to reduce the risk of cardiovascular events in patients with diabetes who underwent PCI.

In the stratified analysis for clinical presentation, there was no previous study comparing the risks of diabetes relative to nondiabetes for cardiovascular events between patients with AMI and non-AMI.[30,31] In the present study, there were no significant interactions between clinical presentation and the risks of diabetes relative to nondiabetes for cardiovascular events. More aggressive interventions for patients with diabetes might be relevant not only in patients with AMI, but also in patients with non-AMI.

STUDY LIMITATIONS. First, selection of potential modifiers of the risk of diabetes for adverse events was arbitrary. We could not deny the presence of other important risk modifiers. Second, there might be residual confounders affecting the risk of diabetes relative to nondiabetes for adverse events, although we conducted extensive multivariable adjustment. Third, diabetes therapy might have been changed during the inclusion period, which began with the use of bare-metal stents and ended with the use of new-generation drug-eluting stents. Moreover, recently developed glucose-lowering drugs, such as glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors, might further reduce the risk of cardiovascular events in patients with diabetes. Fourth, while we sought to assess the impact of baseline diabetes status on clinical outcomes, we did not take into account changes in diabetes status during the follow-up period. Fifth, because of the long inclusion period, MI was adjudicated according to the classical definition of Q-wave MI, not the current universal definition of MI. Sixth, whereas 69.5% of patients with

diabetes had multivessel disease, more than four-fifths of patients underwent PCI. Moreover, the proportion of PCI significantly increased from 2000 to 2013 in Japan, particularly in patients with multivessel disease.[32] The observed interaction between diabetes status and mode of revascularization might not be applicable in patients outside Japan. Finally, follow-up rates were far from complete to enable us to evaluate the effect of diabetes on long-term outcomes for up to 5 years; however, median follow-up duration for survivors were comparable between patients with diabetes (5.9; IQR: 4.9-7.0) and those without diabetes (5.9; IQR: 4.9-7.1).

CONCLUSIONS

The excess risk of diabetes relative to nondiabetes for MACCE was profound in the younger population. Our observation suggests more aggressive interventions for secondary prevention in patients with diabetes might be particularly relevant in younger patients.

ACKNOWLEDGMENTS The authors thank the clinical research coordinators in the Research Institute for Production Development.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was supported by an educational grant from the Research Institute for Production Development (Kyoto, Japan). Dr Yamaji has received a research grant from Abbott Vascular. Dr Shiomi has received honoraria from Abbott Vascular and Boston Scientific. Dr Morimoto has received lecturer's fees from Bristol-Myers Squibb, Daiichi Sankyo, Japan Lifeline, Kowa, Kyocera, Novartis, and Toray; manuscript fees from Bristol-Myers Squibb and Kowa; and has served on the Advisory Board of Sanofi. Dr Ehara has received honoraria from Abbott Vascular, Bayer, Boston Scientific, Medtronic, and Terumo. Dr Furukawa has received honoraria from Bayer, Kowa, and Sanofi. Dr Nakagawa has received research grants from Abbott Vascular and Boston Scientific; and honoraria from Abbott Vascular, Bayer, and Boston Scientific. Dr Kimura has received a research grant from Abbott Vascular; and honoraria from Astellas, AstraZeneca, Bayer, Boston Scientific, Kowa, and Sanofi. All the other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Takeshi Kimura, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, 54 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: taketaka@kuhp.kyoto-u.ac.jp.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The excess adjusted risks of diabetes relative to nondiabetes for MACCE increased with younger age, mainly driven by greater excess adjusted mortality risk of diabetes relative to nondiabetes in younger tertile. No significant interaction was observed between adjusted risk of diabetes relative to nondiabetes for MACCE and other subgroups such as sex, mode of revascularization, and clinical presentation of acute myocardial infarction.

TRANSLATIONAL OUTLOOK: More aggressive interventions for secondary prevention in patients with diabetes might be particularly relevant in younger patients.

REFERENCES

1. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405–412.

2. The Emerging Risk Factors Collaboration, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375(9733):2215–2222.

3. Tancredi M, Rosengren A, Svensson AM, et al. Excess mortality among persons with type 2 diabetes. *N Engl J Med*. 2015;373(18):1720–1732.

4. Rawshani A, Rawshani A, Franzen S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2018;379(7):633–644.

5. Wright AK, Suarez-Ortegon MF, Read SH, et al. Risk factor control and cardiovascular event risk in people with type 2 diabetes in primary and secondary prevention settings. *Circulation*. 2020;142(20):1925–1936.

6. Cavender MA, Steg PG, Smith SC Jr, et al. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the Reduction of Atherothrombosis for Continued Health (REACH) registry. *Circulation*. 2015;132(10):923–931.

7. Ritsinger V, Saleh N, Lagerqvist B, Norhammar A. High event rate after a first percutaneous coronary intervention in patients with diabetes mellitus: results from the Swedish coronary angiography and angioplasty registry. *Circ Cardiovasc Interv*. 2015;8(6):e002328.

8. Takeji Y, Shiomi H, Morimoto T, et al, CREDO-Kyoto PCI/CABG Registry Cohort Investigators. Diabetes mellitus and long-term risk for heart failure after coronary revascularization. *Circ J*. 2020;84(3):471–478.

9. Ehara N, Morimoto T, Furukawa Y, et al. Effect of baseline glycemic level on long-term cardiovascular outcomes after coronary revascularization therapy in patients with type 2 diabetes mellitus treated with hypoglycemic agents. *Am J Cardiol*. 2010;105(7):960–966.

10. Kimura T, Morimoto T, Furukawa Y, et al. Long-term outcomes of coronary-artery bypass graft surgery versus percutaneous coronary intervention for multivessel coronary artery disease in the bare-metal stent era. *Circulation*. 2008;118(suppl 14):S199–S209.

11. Kimura T, Morimoto T, Furukawa Y, et al. Long-term safety and efficacy of sirolimus-eluting stents versus bare-metal stents in real world clinical practice in Japan. *Cardiovasc Interv Ther*. 2011;26(3):234–245.

12. Imai E, Horio M, Nitta K, et al. Modification of the Modification of Diet in Renal Disease (MDRD) study equation for Japan. *Am J Kidney Dis*. 2007;50(6):927–937.

13. Serruys PW, Unger F, Sousa JE, et al, Arterial Revascularization Therapies Study Group. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med*. 2001;344(15):1117–1124.

14. Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-

diabetic people: a population-based retrospective cohort study. *Lancet*. 2006;368(9529):29–36.

15. Sattar N, Rawshani A, Franzen S, et al. Age at diagnosis of type 2 diabetes mellitus and associations with cardiovascular and mortality risks. *Circulation*. 2019;139(19):2228–2237.

16. Zinman B, Wanner C, Lachin JM, et al, EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117–2128.

17. Neal B, Perkovic V, Mahaffey KW, et al, CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644–657.

18. Wiviott SD, Raz I, Bonaca MP, et al, DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347–357.

19. Baber U, Stefanini GG, Giustino G, et al. Impact of diabetes mellitus in women undergoing percutaneous coronary intervention with drug-eluting stents. *Circ Cardiovasc Interv*. 2019;12(7):e007734.

20. Malmborg M, Schmiegelow MDS, Norgaard CH, et al. Does type 2 diabetes confer higher relative rates of cardiovascular events in women compared with men? *Eur Heart J*. 2020;41(13):1346–1353.

21. Kosmidou I, Leon MB, Zhang Y, et al. Long-term outcomes in women and men following percutaneous coronary intervention. *J Am Coll Cardiol*. 2020;75(14):1631–1640.

22. Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med*. 1996;335(4):217–225.

23. Farkouh ME, Domanski M, Sleeper LA, et al, FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med*. 2012;367(25):2375–2384.

24. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet*. 2013;381(9867):629–638.

25. Thuijs D, Kappetein AP, Serruys PW, et al, SYNTAX Extended Survival Investigators. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *Lancet*. 2019;394(10206):1325–1334.

26. Milojevic M, Serruys PW, Sabik JF 3rd, et al. Bypass surgery or stenting for left main coronary artery disease in patients with diabetes. *J Am Coll Cardiol*. 2019;73(13):1616–1628.

27. Wang R, Serruys PW, Gao C, et al. Ten-year all-cause death after percutaneous or surgical revascularization in diabetic patients with complex coronary artery disease. *Eur Heart J*. 2021;43(1):56–67.

28. Head SJ, Milojevic M, Daemen J, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet*. 2018;391(10124):939–948.

29. Farkouh ME, Domanski M, Dangas GD, et al, FREEDOM Follow-on Study Investigators. Long-term survival following multivessel revascularization in patients with diabetes: the FREEDOM Follow-on study. *J Am Coll Cardiol*. 2019;73(6):629–638.

30. Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) registry. *Circulation*. 2000;102(9):1014–1019.

31. Guan S, Xu X, Li Y, et al. Impact of diabetes mellitus on antithrombotic management patterns and long-term clinical outcomes in patients with acute coronary syndrome: insights from the EPICOR Asia study. *J Am Heart Assoc*. 2020;9(22):e013476.

32. Shiomi H, Morimoto T, Furukawa Y, et al. Coronary revascularization in the past two decades in Japan (from the CREDO-Kyoto PCI/CABG Registries Cohort-1, -2, and -3). *Am J Cardiol*. 2021;153:20–29.

KEY WORDS coronary artery bypass graft, diabetes, percutaneous coronary intervention

APPENDIX For supplemental figures and tables and lists of participants, please see the online version of this paper.